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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/651,290	08/30/2000	Marcin S. Filutowicz	P00154US/13238/00016	2591

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EXAMINER

FORD, VANESSA L

ART UNIT PAPER NUMBER

1645

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11

Please find below and/or attached an Office communication concerning this application or proceeding.

File Copy

Office Action Summary

Application No. 09/651,290	Applicant(s) FILUTOWICZ, MARCIN S.	
Examiner Vanessa L. Ford	Art Unit 1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 04 September 2001.
- 2a) This action is FINAL.
- 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 1-12, 14-27 and 29-30 is/are pending in the application.
 - 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 1-12, 14-27 and 29-30 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claims _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on _____ is/are objected to by the Examiner.
- 11) The proposed drawing correction filed on _____ is: a) approved b) disapproved.
- 12) The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

- 13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 - a) All b) Some * c) None of:
 - 1. Certified copies of the priority documents have been received.
 - 2. Certified copies of the priority documents have been received in Application No. _____.
 - 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

- 15) Notice of References Cited (PTO-892)
- 16) Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 17) Information Disclosure Statement(s) (PTO-1449) Paper No(s) 4.
- 18) Interview Summary (PTO-413) Paper No(s). _____
- 19) Notice of Informal Patent Application (PTO-152)
- 20) Other:

DETAILED ACTION

1. Applicant's election of Group I, claims 1-12, 14-17 and 29-30 in Paper No. 8 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Claims 13 and 28 have been cancelled.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-12, 14-17 and 29-30 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to an antibacterial agent which comprises a non-pathogenic bacterial cell harboring at least one transmissible plasmid comprising: an origin of replication wherein the initiation of replication at the origin is negatively controlled by a plasmid replication repressor, an origin of transfer and optionally, at least one screenable marker gene and a pharmaceutical preparation comprising the antibacterial agent.

The specification generically claims an antibacterial agent that comprises a non-pathogenic donor bacterial cell harboring at least one transmissible plasmid comprising an origin of replication, an origin of transfer and optionally at least one screenable gene marker. The claimed invention further includes a plurality of microorganisms of which the donor cell or recipient cell can be obtained. The specification does not provide substantive evidence that the claimed antibacterial agent can maintain stability or that the pharmaceutical preparation comprising the antibacterial agent is capable of treating bacterial infections. This demonstration is required for the skilled artisan to be able to use the claimed invention for the intended purpose of treating bacterial infections. Without this demonstration, the skilled artisan would not be able to reasonably predict whether the claimed invention could survive *in vivo* use or whether the artisan would be able to predict if the administration of the claimed pharmaceutical preparation, would be able to treat bacterial infections.

There are several factors that contribute to the stability of plasmids that are well known in the art. These factors include: 1) the ability of conjugative transfer within and between genera, 2) essential components required to ensure stabilization 3) mating pair stabilization and 4) compatibility between the donor and recipient cell. The ability to reasonably predict the capacity of plasmids to be conjugatively transferred within genera and especially between genera, maintain stability is problematic. This is evidenced by Ambrozic et al, *Microbiology (ENGLAND)*, February 1998, 144(Pt 2), p. 343-352). Ambrozic et al teach that conjugal transfer was demonstrated with low frequency to *Klebsiella pneumoniae* suggesting that a natural barrier effectively bars

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transfer. Specific sequences are also required for the complete stabilization of plasmids. For example, Roberts et al, (*Journal of Bacteriology*, November 1990, 172 (11), p. 6204-6216) teach that one of the regions responsible for stable inheritance of the broad host range plasmid RK2 is contained within the PstI C fragments. Robert et al teach that the PSTI C fragment itself is not required for stabilization activity, however the PSTI C fragment encodes a multimer resolution system which required adjacent sequence to maintain complete stabilization. Mating stabilization during conjugative transfer between the donor and recipient cell is also required. Klimke et al, (*Journal of Bacteriology*, August 1998, 180 (16), p. 4036-4043) teach that mating stabilization occurs during conjugative transfer whereby the donor cell and recipient cells form a tight junction which requires pili as well as TraN and TraG (proteins involved in mating pair stabilization) in the donor cell. Klimke et al teach that the TraN and not the F pili appears to interact with OmpA and LPS moieties during conjugation, resulting in mating stabilization. Klimke et al further teach that this is the first step in efficient mobilization of DNA. Compatibility between the donor cell and the recipient cell is also necessary. This is further evidenced by Rahal et al, (*Annales de microbiologie (FRANCE)*, May-June 1978, 129 (4), p. 409-414). Rahal et al teach that very few multi-resistant strains of *Vibrio cholerae* have been isolated this may be due to a high frequency of plasmids being lost due to the incompatibility of groups. Since genetic mutations are used to determine the structural and functional properties of the claimed antibacterial agent and pharmaceutical composition the predictability of which changes or mutations can be tolerated in the host and still retain similar activity requires a knowledge of and guidance

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with regard to which mutations can be made in the plasmid wherein stability will be maintained. The cited references have shown that unpredictability exists regarding plasmid stability. Therefore, it can be concluded that undue experimentation would be required to make and use the claimed antibacterial agent without proper guidance.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the pharmaceutical preparation commensurate in scope with these claims. The specification fails to teach how to make and use the claimed pharmaceutical preparation. The term "pharmaceutical" encompasses the ability of the specific antigen to induce protective immunity to a host. The specification does not disclose how to formulate the pharmaceutical preparation or what dosages are required to treat a patient with a bacterial infection? The specification further does not disclose whether the antibacterial agent can survive the mouth, stomach or intestines without being degraded or if the antibacterial agent is capable of reach the target organs necessary to treat a particular bacterial infection. Therefore, it is unclear as to how to formulate a pharmaceutical preparation comprising the antibacterial agent which will treat any bacterial infection.

Factors to be considered in determining whether undue experimentation is required, are set forth in In re Wands 8 USPQ2d 1400. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state

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of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims.

Applying the above test to the facts of record, it is determined that 1) no declaration under 37 C.F.R. 1.132 or other relevant evidence has been made of record establishing the amount of experimentation necessary, 2) insufficient direction or guidance is presented in the specification with respect to selecting a stable antibacterial agent and pharmaceutical preparation that would achieve a desired level of success when administered to a patient with a bacterial infection that is capable of treating that bacterial infection, 3) there are limited working examples which suggest the desired results of an antibacterial agent that is to be used in a pharmaceutical preparation to treat any bacterial infection, 4) the relative skill of those in the art is commonly recognized as quite high (post - doctoral level), and the lack of predictability in the field to which the invention pertains is recognized in the art as evidenced by the cited prior art.

In view of all of the above, in view of the lack of predictability in the art, it is determined that it would require undue experimentation to make and use the claimed invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 14-15 are indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 14 and 15 recite

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“pre-determined route of administration” it is unclear as to what the applicant is referring?

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

4. Claims 1-12 and 16-27 are rejected under 35 U.S.C. 102(b) as anticipated by Metcalf et al (*Plasmid*, 35, 1996, p. 1-13).

Claims 1-12 and 16-27 are drawn to an antibacterial agent which comprises a non-pathogenic bacterial cell harboring at least one transmissible plasmid comprising: an origin of replication synthesizing the plasmid in a bacterial cell wherein the initiation of replication at the origin is negatively controlled by a plasmid replication repressor, an origin of transfer from which conjugative transfer of the transmissible plasmid initiates from the donor cell to at least one recipient cell and optionally, at least one screenable marker gene wherein the donor cell further comprises one or more transfer genes conferring upon the donor cell the ability to conjugatively transfer the transmissible plasmid to the recipient cell and wherein the donor cell produces the plasmid replication repressor and further wherein at least one recipient cell is a pathogenic bacterium that does not produce the plasmid replication repressor.

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Metcalfe et al disclose the conditionally replicative and conjugative plasmids carrying $\text{lacZ}\alpha$ for cloning, mutagenesis and allele replacement in bacteria (see the Title). Metcalfe et al disclose new cloning vectors that have R6K γ DNA replication origin ($\text{oriR}_{\text{R6K}\gamma}$) so that they replicate only in bacteria supplying the Π replication protein (encoded by pir) and they can be maintained at low or high plasmid copy number by using *Escherichia coli* strains encoding either wild-type or mutants forms of Π . Metcalfe et al disclose that the vectors also carry the RP4 transfer origin (oriT_{RP4}) so they can be transferred by conjugation to a broad range of bacteria. Metcalfe et al disclose that plasmids are especially useful for allele replacement experiments because they also encode a positive counterselective marker (page 2). Limitations such as for treating a patient "for a bacterial infection" are being viewed as intended use limitations.

Since the Office does not have the facilities for examining and comparing applicant's antibacterial agent and pharmaceutical preparation with the antibacterial agent and pharmaceutical preparation of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the antibacterial agent and pharmaceutical preparation of the prior art does not possess the same material structural and functional characteristics of the claimed antibacterial agent and pharmaceutical preparation). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

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5. Claims 14-15 and 29-30 are rejected under 35 U.S.C. 102(e) as anticipated by MacInnes et al (*US Patent No. 6,019,984, filed December 23, 1996*).

Claims 14-15 and 29-30 are drawn to pharmaceutical preparation which comprises the antibacterial agent of claim 1.

MacInnes et al disclose novel bacterial preparations containing one or more isolated and purified strain of a microorganism which produces one or more RTX toxins wherein the strain has at least one RTX toxin which is substantially cell-associated (see the Abstract). MacInnes et al disclose that bacterial preparations of their invention may be prepared by using gene transfer techniques which include antibacterial agent which comprises a non-pathogenic bacterial cell harboring at least one transmissible plasmid comprising: an origin of replication synthesizing the plasmid in a bacterial cell wherein the initiation of replication at the origin is negatively controlled by a plasmid replication repressor, an origin of transfer from which conjugative transfer of the transmissible plasmid initiates from the donor cell to at least one recipient cell and optionally, at least one screenable marker gene wherein the donor cell further comprises one or more transfer genes (columns 11-12 and column 33-34). MacInnes et al disclose that a nucleic acid molecule containing the antisense sequences may be introduced into the microorganism using conventional techniques such as transformation, transfection, infection, conjugation and physical techniques such as electroporation.

Since the Office does not have the facilities for examining and comparing applicant's antibacterial agent and pharmaceutical preparation with the antibacterial agent and pharmaceutical preparation of the prior art, the burden is on the applicant to

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show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the antibacterial agent and pharmaceutical preparation of the prior art does not possess the same material structural and functional characteristics of the claimed antibacterial agent and pharmaceutical preparation). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

Pertinent Prior Art

6. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure (*Toukdarian et al, Gene 223, 1998, p. 205-211*).

Status of Claims

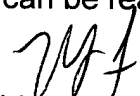
7. No claims are allowed.

Conclusion

8. Any inquiry of the general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Office Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for the Group 1600 is (703) 308-4242.

Any inquiry concerning this communication from the examiner should be directed to Vanessa L. Ford, whose telephone number is (703) 308-4735. The examiner can normally be reached on Monday – Friday from 7:30 AM to 4:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached at (703) 308-3909.


Vanessa L. Ford
Biotechnology Patent Examiner
November 8, 2001


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